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Familial Autoimmunity and the Idiopathic Inflammatory Myopathies

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Many lines of evidence suggest that autoimmune diseases result from chronic immune activation following environmental exposures in genetically susceptible individuals. A genetic basis for autoimmunity is supported by twin and family studies, candidate gene investigations, animal models, and whole genome microsatellite scans. These findings predict, and clinical observations support, familial clustering of a number of individual autoimmune diseases, notably lupus, multiple sclerosis, type-1 diabetes mellitus, rheumatoid arthritis, and recently the idiopathic inflammatory myopathies. Yet, not only is the same autoimmune disease increased in prevalence in pedigrees of persons affected with a given disorder, but other autoimmune diseases are as well. We review these data and propose a hypothesis consistent with these findings. This model posits that a rheumatic disease, as currently classified, is actually composed of a number of elemental disorders. Each of these is defined by the minimal necessary and sufficient environmental exposures and genes that result in a pathology leading to a given sign-symptom complex.

Introduction

A diverse array of diseases, that may involve a single organ system or multiple systems, result from pathologic immune responses to self-tissues. These disorders, known as autoimmune diseases, are chronic debilitating entities that likely affect more than 5% of the population and appear to be increasing in prevalence [1,2]. Despite intense investigation over decades, their etiology and pathogenic mechanisms remain poorly understood. Different investigative approaches suggest, however, that autoimmune diseases maybe the result of chronic immune activation induced by environmental exposures in genetically susceptible individuals [3,4].

Although much remains to be learned about the pathogenesis of autoimmune diseases, recent studies have identified several probable genetic risk factors for many human immune-mediated disorders [4–7,8••]. While little is known about environmental risk factors, possible triggers for selected autoimmune diseases include a number of infectious agents, drugs, foods, biologics, occupational, and other exposures [9–14]. The identification of genetic risk factors predicted a familial pattern for some autoimmune diseases. In fact, anecdotal reports, as well as case-control and other studies, have described a number of examples of families in which multiple members are affected by the same or different autoimmune diseases [15]. Here, we summarize these data, which primarily relate to multiple sclerosis (MS), insulin-dependent (type-I) diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) in the context of recent similar findings in the idiopathic inflammatory myopathies (IIM).

Evidence for a Role of Genetic Factors in the Pathogenesis of Autoimmune Disease

Evidence supporting a role for genetic factors in the etiology of autoimmune disease comes from case reports, family studies, animal model investigations, candidate gene case-control studies, and recently whole genome scans (Table 1). It is interesting that many of the syndromes that we recognize as autoimmune diseases today were initially described some time ago. Some of the earliest case reports of likely autoimmune diseases occurred in the 10th century [16]; evidence of MS dates to the late 14th century [17]. SLE was first clinically described as an entity by William Osler [18], but the medical use of the word "lupus" first appeared in the 10th century in St. Martin's biography [16]. Diabetes mellitus was recognized as a disorder some 2000 years ago by Hindu physicians Charaka and Sushruta, and it is they who may have been the first to recognize that genetic (familial) and environmental (dietary) factors played a role in the development of the disease characterized by "honey urine" [19,20].

Further confirmation that genetics play a role in autoimmune diseases came from case reports of familial autoimmunity [21–25]. Based on these findings, twin studies were initiated that showed concordance rates for the same autoimmune disease in monozygotic twins, who share 100% of genes, to be significantly higher than the concordance rates in dizygotic twins, who share on average 50% of genes (Table 1). Nonetheless, the fact that the con-

Table 1. Studies suggesting a genetic role in the pathogenesis of autoimmune diseases

Case reports of two or more family members with the same autoimmune disease

Disease	Family members affected	Comments	Reference
SLE	Two pairs of brothers with SLE	Supports hereditary factor in pathogenesis	Spector *et al.* [22]
MS	Mother and son	Probably the first reported case of familial MS	Eichhorst *et al.* [21]
IDDM	Canadian Mennonite kindred study	Strong support for familial aggregation of IDDM	Jaworski *et al.* [25]
RA	Four generations of women in one family	First publication to define the hereditary nature of RA	Deighton *et al.* [23] Lawrence *et al.* [24]

Twin studies of concordance of the same autoimmune disease

Disease	Study design	Concordance in MZ twins, %	Concordance in DZ twins, %	Reference
SLE	Volunteer twin registry	24	2	Deapen *et al.* [74]
MS	Twin survey	31	5	Sadovnick *et al.* [75]
IDDM	Volunteer twin registry	53	11	Kyvik *et al.* [76]
RA	Volunteer twin registry	15	4	Silman *et al.* [77]

Family investigations

Disease	Study design	Comments	Reference
SLE	Lupus relatives versus control relatives	SLE seen in 3.9% in SLE relatives versus 0.3% in controls	Lawrence *et al.* [26]
MS	Data from 815 MS cases and 11,345 relatives	MS prevalence 30–50 times higher in pedigrees of MS subjects compared with the general population	Sadnovick *et al.* [28] Sadnovick *et al.* [29]
IDDM	Swedish childhood diabetes study	Associated IDDM with familial autoimmunity	Dahlquist *et al.* [30]
RA	Studied 43 Caucasian RA pedigrees	RA proband relatives have higher risk of RA and other AD	Lin *et al.* [27]

Candidate gene studies

Disease	Study design	Gene	Comments	Reference
SLE	Family studies	HLA DRB1*03	*P*corr. <10–5 compared with controls	Heward *et al.* [78]
MS	Case-control	HLA DRB1*02, DQA1*0102,DQB1*0 602	HLA explains 17%–62% of genetic etiology	Yao *et al.* [79] Heward *et al.* [78] Haines *et al.* [80•]
IDDM	Case-control	HLA DRB1*03,*04,DQA1, DQB1	95% of patients have either DR3,4	Heward *et al.* [78] Todd *et al.* [81] Tisch *et al.* [82]
RA	Sib pair study	HLA DRB1*04	LOD score of 2.6 (*P*=0.0003)	Heward *et al.* [78]

Whole genome microsatellite scans

Disease	Study design	Loci	LOD	Reference
SLE	Sib pair	6p11-p21;16q13; 14q21-23;20p12	3.9;3.6;2.8;2.6 (respectively)	Gaffney *et al.* [83]
MS	Microsatellite scan	6p21;17q22-24	2.8 (λs=1.5); 2.7(λs=1.7)	Sawcer *et al.* [84] Kuokkanen *et al.* [85]
IDDM	Microsatellite scan	6p21(IDDM1)	λs=2.4	Cordell *et al.* [86] Todd *et al.* [87]
RA	Genome scan	3q13	*P*=0.001 compared other RA patients	Cornelis *et al.* [88]

AD—autoimmune disease; DZ—dizygotic; HLA—human leukocyte antigen; IDDM—insulin-dependent (type 1) diabetes mellitus; lod—logarithm of odds score; MS—multiple sclerosis; MZ—monozygotic; Pcorr—corrected P value; RA—rheumatoid arthritis; SLE—systemic lupus erythematosus; λ—relative risk in siblings+A26

cordance rates in monozygotic twins were seldom over 40% suggested that these diseases are multifactorial in their etiology. Monozygotic twins are genetically identical, but differences in environmental exposures do modify the evolution of their immune systems resulting in variations in immunocyte distributions and receptor expression soon after birth.

Family and other studies indicate that certain genetic predispositions increase an individual's risk of developing some autoimmune diseases [26–30]. Candidate gene studies have pointed to the HLA region on human chromosome 6 as having the strongest associations with many immune-mediated diseases [7,31–33]. Certain HLA genes, however, may actually serve a protective role against the development of some autoimmune diseases [34–36]. Although it is clear that a number of other genes, in addition to HLA genes, are likely necessary, but not sufficient, for the development of autoimmunity. A polygenic predisposition, involving perhaps a number of genes, with the additional requirement of exposure to one or more environmental triggers, is apparently responsible for the onset and perpetuation of these disorders [3,4,37,38••,39). Non-HLA loci implicated as risk factors for autoimmunity include regions encoding immunoglobulins, cytokines, and their receptors, autoantigens, and T-cell receptors [37,40–43].

Another approach that has been useful in defining the genes for single gene disorders involves analyses of linkage of microsatellite markers to clinical phenotypes [44]. Over 40 genetic loci that appear to predispose to autoimmunity have been identified in mice and humans using microsatellite markers that cover the entire genome, and a recent meta-analysis demonstrates clustering of these loci in 18–20 chromosomal regions, suggesting common genetic risk factors for many autoimmune diseases [38••,45•].

Evidence for a Role of Genetic Factors in the Pathogenesis of Idiopathic Inflammatory Myopathies

Since the first case of polymyositis was recognized and reported by Hans Unverricht over 100 years ago [46], much has been learned about the growing number of syndromes that comprise the IIM [47]. Although their rarity and heterogeneity have inhibited progress in understanding their pathogenesis, current evidence suggests that gene–environment interactions likely contribute to the development of these increasingly recognized diseases [4,9]. As is the case for other autoimmune conditions, the genetic basis for IIM is supported by reports of multiple members of the same family having myositis as well as cohort and case-control investigations of candidate genes.

At present, 33 families have been reported in which two or more members have developed myositis (Table 2). These families have included cases of polymyositis, dermatomyositis, and inclusion body myositis. The earliest known reported cases of familial IIM were published in the 1950s [48–50]. Further investigations of familial aggregations of IIM led to many more reports of myositis occurring in families (Table 2).

Of these investigations, the most comprehensive study of familial IIM has been a recent report of 36 affected and 28 unaffected members of 16 unrelated families in which at least two first-degree living relatives had probable or definite IIM [51•]. In this study, Rider *et al.* [15] described the clinical, serologic, and immunogenetic features of these families, and compared the familial IIM cases with a comparison group of 181 patients with sporadic IIM. From the 16 families studied, HLA DRB1*0301 was a weaker risk factor for familial IIM compared with sporadic IIM (etiologic fraction 0.35 versus 0.51 for sporadic IIM). Of interest, DQA1*0501, a risk factor for sporadic IIM [52•], was not a significant risk factor for myositis in the familial cases, despite the linkage disequilibrium that exists between HLA DRB1*0301 and DQA1*0501. The strongest genetic risk factor for familial IIM was homozygosity at the DQA1 locus (seen in 57% of cases, odds ratio of 4.2, corrected P=0.002), a risk factor not seen in sporadic IIM. The frequencies of a number of clinical features were similar in both groups, but the prevalence of myositis-specific autoantibodies was lower in the familial group as compared with the sporadic group.

Of interest, the same clinical form of myositis was usually found within a given multiplex family. For example, in family 5, all three affected members had polymyositis and in family 15, all six affected members had inclusion body myositis [51]. This study clearly demonstrated that familial weakness is not always due to inherited metabolic or dystrophic myopathies, but rather can be due to familial IIM. These data, taken together with other data, suggest that multiple genetic risk factors, and as yet unidentified environmental risk factors, are likely important in the etiology of the myositis syndromes.

To assess the role of possible environmental triggers for myositis within a multiplex IIM family, we compared the differences in time of onset to differences in age of onset of myositis in each of the 22 pedigrees for which such data were available (Fig. 1). This analysis showed that the differences between the time of myositis onset (median 1.1, range 0.04–11.7 years) was significantly less than the differences in age at myositis onset (median 7.5, range 0.04–33 years, P=0.006 by the Mann-Whitney test). These data are consistent with the hypothesis that several genetically susceptible family members may be been exposed to the same environmental agent within a short time frame that may have triggered IIM in those individuals.

Candidate gene approaches have also been used to define genetic risk factors for IIM (Table 3). The HLA-A1;B8;Cw7;C4A*Q0;DRB1*0301;DQA1*0501 haplotype, which is a risk factor for many autoimmune diseases including SLE and myasthenia gravis [53], also is a risk factor for many forms of Caucasian, Hispanic, and African-American myositis [52,54–56]. Some racial groups in dif-

Table 2. Chronology of reported multiplex families that have two or more members with idiopathic inflammatory myopathy (IIM).

IIM types	Family members affected	Comments	Reference
JDM-JDM	"Mirror-image twins"	The onset of the disease was 1 year apart	Woodwedge *et al.* [48]
JDM-JDM	Two siblings	The onset of the disease was about 8 weeks apart	Winkler *et al.* [49]
DM-DM	Two adult siblings	The onset of the disease was 4 years apart	Christianson *et al.* [50]
JDM-JDM	Two cousins	The onset of the disease was 2 years apart	Lambie *et al.* [89]
PM-JDM	Father and daughter	The onset of the disease was 6 years apart	Lewkonia *et al.* [90]
JDM-JDM	Identical twins	Onset within 2 weeks of each other after URIs	Harati *et al.* [91]
JDM-JDM-DM	First cousins and uncle	Patients living in different towns; genetic factors may be more important	Hennekam *et al.* [92]
IBM-IBM	Two siblings	Identified in one Iranian-Kurdish Jewish family	Massa *et al.* [93]
IBM-IBM	Two adult sisters	Identified in another Iranian-Kurdish Jewish family	Massa *et al.* [93]
PM-PM-PM-PM	Four family members	Concurrent onset, possible association with local rodents	Garcia-de la Torre *et al.* [94]
IBM-IBM-IBM-IBM-IBM-IBM	Kindred study	First reported case of possible autosomal dominant inheritance	Neville *et al.* [95]
IBM-IBM	Mother, daughter, and son	First reported case in Spain	Andreu *et al.* [96]
IBM-IBM	Two adult sisters	Evidence of hereditary IBM and hereditary glucocorticoid insensitivity	Naumann *et al.* [97]
IBM-IBM	Two adult brothers	Parents were unaffected and offspring were spared	Sivakumar *et al.* [98]
IBM-IBM	Two adult brothers	Only one generation was affected, parents and offspring spared	Sivakumar *et al.* [98]
IBM-IBM-IBM	Three siblings	Two African-American brothers and their sister were affected	Sivakumar *et al.* [98]
DM-DM	Case-report	Mother and daughter with DM and another daughter with DM rash only	Andrews *et al.* [99]
IBM-IBM	Identical twin brothers	Onset was 2 years apart	Amato *et al.* [100]
JDM-JDM	Identical twin sisters	Onset was within 3 months, identical pattern of calcification in both	Rider *et al.* [51•]
JDM-JDM	Identical twin sisters	Onset was within 2 months, very similar disease course	Rider *et al.* [51•]
JDM-JDM	Identical twin sisters	Onset was within 12 months	Rider *et al.* [51•]
DM-JDM	Two sisters	Onset was within 11.7 years	Rider *et al.* [51•]
DM-DM	Mother and daughter	Onset was within 1 year	Rider *et al.* [51•]
DM-DM	Father and son	Onset was within 6.7 years	Rider *et al.* [51•]
PM-PM	Brother and sister	Onset was within 4 months, two of seven sibs (all had DQA1*0501)	Rider *et al.* [51•]
PM-PM	Brother and sister	Onset was within 4.5 years	Rider *et al.* [51•]
PM-PM-PM	Two sisters and one brother	Onset was within 8.7 years	Rider *et al.* [51•]
PM-PM	Parent and child	Onset was within 4 months	Rider *et al.* [51•]
PM-PM	Father and daughter	Onset was within 2.3 years	Rider *et al.* [51•]
PM-PM	Two female cousins	Onset was within 1.25 years	Rider *et al.* [51•]
IBM-IBM-PM?-IBM	One parent and two children	Patient with PM? may have had undiagnosed IBM	Rider *et al.* [51•]
IBM-IBM	Identical twin brothers	Involved the quadriceps and volar forearm muscles	Amato *et al.* [100]
DM-DM	Grandmother and granddaughter		Cassidy *et al.* [101]

AD—autoimmune disease; DM—dermatomyositis; IBM—inclusion body myositis; IIM—idiopathic inflammatory myopathies; JDM—juvenile dermatomyositis; JIIM—juvenile IIM; JRA—juvenile rheumatoid arthritis; PM—polymyositis; RA—rheumatoid arthritis; URI—upper respiratory infection.

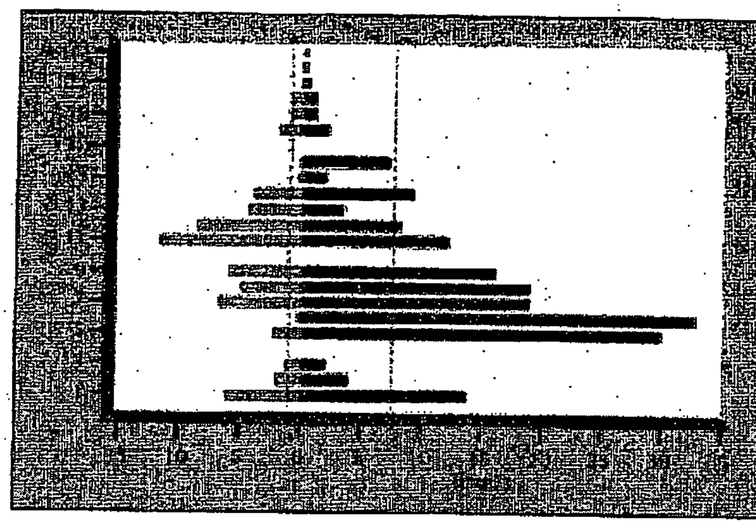

Figure 1. Comparison of the differences in the time of onset (left) with the age of onset (right) of family members with IIM. Families 18–23 each contain monozygotic twins affected with IIM, families 11–16 have non-twin siblings affected with IIM, families 5–9 have parents and offspring affected with IIM, and families 1–3 have more distant relatives affected with IIM. The differences in the time of onset of myositis (median indicated by the dotted line is 1.1, range 0.04–11.7 years) were significantly less (P=0.006 by the Mann-Whitney test) than the differences in age at myositis onset (median indicated by the dotted line is 7.5, range 0.04–33 years) in the pedigrees. These data are consistent with the hypothesis that genetically susceptible family members shared common environmental exposures within a short timeframe that may have triggered IIM in that family.

ferent parts of the world, however, appear to have different genetic risk factors for myositis. Although the major known risk factors for US Caucasian patients are HLA alleles on chromosome 6 sharing a common DRB1 first hypervariable region motif [52•]. Korean patients with myositis have no HLA risk factors, but a unique protective factor, DRB1*14 in patients without myositis-specific autoantibodies [36]. Although no immunoglobulin Gm phenotypes, encoded on chromosome 14, are risk factors in either population, the Gm 21 allotype is a protective factor only for Koreans, and not Caucasians with myositis [36]. Also, although the major clinical groups of the IIM (*ie*, PM, DM, and IBM) share genetic risk factors, each serologic group has a distinct risk factor [54]. Certain environmental exposure groups also appear to differ in genetic risk factors. In Caucasians, HLA DR4 appears to be over represented in those who develop myositis after D-penicillamine [57–60], whereas DQA1*0102 is significantly more frequent in women who develop myositis after silicone implants compared with those with idiopathic myositis [61].

Different Autoimmune Diseases Can Occur Within the Same Family

Clinical experience, and the finding of common genetic risk factors for several autoimmune conditions [38], implied that many autoimmune disorders might be increased in family members of individuals with different autoimmune diseases. To test this hypothesis, several studies have assessed if autoimmune diseases other than those in the proband were present in blood relatives in frequencies higher than expected in the general population. Investigations of pedigrees of probands with SLE, MS, IDDM, and RA all have supported the hypothesis that multiple autoimmune diseases appear in certain families [27,62–64].

Evidence has also been obtained that suggests that this same phenomenon is true for the IIM. An evaluation of histories from juvenile IIM patients suggested that there is a high frequency of autoimmune diseases in these families, with 28 of the 75 first-degree relatives exhibiting one or more autoimmune diseases [65]. The diseases, which were described in 37% of the first-degree relatives, were myositis, IDDM, thyroid disease, SLE, scleroderma, and psoriasis. Another study by Pachman *et al.* [66•] assessed histories of autoimmune disease in families of 80 JDM patients, families of 40 juvenile rheumatoid arthritis (JRA) subjects, and families of 23 normal healthy geographically matched controls. This study suggested that JRA patients had significantly more relatives with a history of RA and pernicious anemia than controls, but a similar increase was not seen in the JDM families. A different approach was taken in another study, which compared the frequency of familial autoimmunity in first-degree relatives of familial IIM patients with that in first-degree relatives of sporadic IIM patients, and showed that both had a high prevalence of autoimmune diseases [51•]. Of interest, however, pedigrees of sporadic IIM probands had a higher frequency of autoimmunity compared with those of familial IIM probands (61% versus 37% respectively, P=0.005). Unfortunately, all these studies had limitations in that the diagnosis of autoimmunity in family members was based upon a history from the affected proband rather than a direct evaluation of all the family members themselves.

To address this question directly, and attempt to minimize the limitations of many prior family studies, Ginn *et al.* [67••] performed a prospective case-control study that evaluated all family members directly. The study group consisted of 21 consecutive IIM patients who presented to the NIH Clinical Center and fulfilled criteria for either probable or definite disease [68,69], and their 151 first-degree relatives. The control group consisted of age-, sex-, and race-matched subjects, who were referred to the NIH but did not exhibit any evidence of autoimmunity, and their 143 first-degree relatives. This study found a significantly higher

Table 3. Human leukocyte antigen (HLA) associations in the idiopathic inflammatory myopathies (IIM)

IIM type (race)	HLA associations	Comments	Reference
All IIM (C)	A1, B8, DR3, C4A QO, DQA1*0501, (DQ2)	Caucasian haplotype risk factor for many autoimmune diseases	Arnett et al. [52•] Pachman et al. [102] Hirsch et al. [103] Moulds et al. [104]
All IIM (AA)	B7, C4A, QO	B7 seen in 67% of African Americans compared with 26% in controls	Hirsch et al. [103] Moulds et al. [104]
All IIM (J)	B7	Seen in 20.2% of Japanese compared with 6.9% in controls	Furuya et al. [105]
Familial IIM	DQA1 homozygosity	Seen in 57% of 36 patients vs. 24% of 181 controls	Rider et al. [51•]
Clinical groups			
PM (C)	A1, B8, DR3, DQA1*0501 (DQ2)	A Caucasian haplotype	Pachman et al. [102] Behan et al. [106] Mierau et al. [107]
PM (AA)	B7, DRw6	6/9; 7/9 respectively in African Americans	Hirsch et al. [103]
PM (J)	CW3	Seen more in PM than in DM in the Japanese	Furuya et al. [105]
DM (C)	DR3	Seen in 47% of 55 patients in adult Caucasians	Koffman et al. [108]
DM (J)	DRB1*08	Increased in Japanese PM and DM	Furuya et al. [105]
CTM (C)	DR3	Seen in 32% of 24 patients in adult Caucasians	Love et al. [108]
IBM	DRB1*03, DRB3, DQB2	This haplotype was present 77% of sporadic IBM patients	Koffman et al. [109]
JDM	B8, DQA1*0501	B8 is a risk factor in Caucasian, 0501 is an inter-racial risk factor	Pachman et al. [110] Friedman et al. [111] Reed et al. [112] Reed et al. [113]
JDM	DQA1 0501	Shown to be a risk factor by transmission disequilibrium	Reed et al. [113]
Serologic groups			
without MSA	DR3	Seen in 37% of 90 Caucasian patients	Love et al. [108]
Without MSA	DR*14	A protective factor in Koreans	Rider et al. [36]
Anti-synthetase	DR3, DRw6, DRw52, DQA1*0501	Risk factors for anti-Jo-1 may differ from those for other synthetases	Arnett et al. [52••] Love et al. [108] Arnett et al. [114] Goldstein et al. [115]
Anti-SRP	DR5, DRw52	DR5 seen in 57% of 7 patients, DRw52 in 100% of 7 patients	Love et al. [108]
Anti-Mi-2	DR7, DQA1*0201, DRw53	31% homozygosity at DR7 versus 0% in Mi-2 negative patients	Mierau et al. [107]
Anti-MAS	DR4, DQA1*01,*03, DRw53	Two of two patients had these alleles	Love et al.[108] Love et al. [108]
Anti-PM/Scl	DR3, DQA1*0501	Frequent serologic group in Poland	Hausmanowa et al. [54]
Anti-Ku	DR3, DQA1*0501	In Polish patients with overlap syndromes	Hausmanowa et al. [54]
Environmental groups			
D-penicillamine	DR2	Two Caucasian DM patients reported receiving drug for RA	Halla et al. [58]
D-penicillamine	B18, B35, DR4	Eight Australian cases with RA	Carroll et al. [59]
D-penicillamine	DR2, DQw1	In Indian patients	Taneja et al. [60]
Silicone breast implants	DQA1*0102	In 9/12 (75%) patients vs.19.7% of normals and 16.3% IIM, $P<.0001$	Love et al. [61]

AA—African American; AD—autoimmune disease; C—Caucasian; DM—dermatomyositis; IBM—inclusion body myositis; IIM—idiopathic inflammatory myopathies; J—Japanese; JDM—juvenile dermatomyositis; JRA—juvenile rheumatoid arthritis; PM—polymyositis; RA—rheumatoid arthritis.

Table 4. Age and gender distributions of family members with autoimmune disease / total number of first-degree relatives, in a study of families of IIM and control probands*

	IIM proband pedigrees		Control proband pedigrees	
Age, y	**Male**	**Female**	**Male**	**Female**
5-19	0/8	0/4	0/8	0/0
20-39	2/28	6/26	0/19	1/22
40-59	2/20	7/17	1/15	1/23
>60	3/23	13/25	1/27	3/29
Totals	7/79	26/72	2/69	5/74
	Overall total = 33/151†		Overall total = 7/143†	

* Subjects less than 5 years of age were excluded from the study. At the beginning of the study, a consensus list of disorders considered to be autoimmune diseases for evaluation of the subjects in this study included: autoimmune thyroid disease, whether Hashimoto's thyroiditis or Grave's disease; Coomb's positive hemolytic anemia, and pernicious anemia; eosinophilic fasciitis; Goodpasture's syndrome, proliferative or membranous nephritis; IDDM not associated with obesity or pregnancy; idiopathic inflammatory myopathies; idiopathic myocarditis; idiopathic pulmonary fibrosis; idiopathic thrombocytopenic purpura; idiopathic uveitis; inflammatory bowel disease, Crohn's disease or ulcerative colitis; multiple sclerosis; myasthenia gravis; pemphigus; primary biliary cirrhosis or chronic active hepatitis; psoriasis; RA or JRA; sarcoidosis; systemic sclerosis; Sjögren's syndrome; SLE; undifferentiated or mixed connective tissue disease; vasculitides and vitiligo.
† Odds ratio without regression adjustment 5.5, 95% CI, 2.3–12.9, $P<0.001$
IIM—idiopathic inflammatory myopathies.
(*Adapted from* Ginn *et al.* [67••].)

prevalence of autoimmune diseases in the IIM proband pedigrees compared with pedigrees of the controls (Table 4). As expected, more women than men were affected, and the frequency of autoimmune disease increased with age. Another finding from this study, which paralleled prior investigations of this sort [27,51•], was that the types of autoimmune diseases seen in the IIM pedigrees were present in frequencies similar to those seen in the general population. Genetic modeling studies showed that a non-Mendelian polygenic inheritance pattern for autoimmune disease was most consistent with these data. Overall, this study and others like it support the concept that one could begin with a cohort of subjects with any given autoimmune disease and likely find an increased number of other autoimmune diseases in pedigrees of that cohort of patients in a prevalence distribution that parallels the prevalence of autoimmune diseases in the general population.

Conclusions

The multifactorial nature of autoimmune diseases has inhibited the understanding of the mechanisms that initiate and sustain them. Autoimmune syndromes are believed to arise, however, from a complex and ill understood interplay of predisposing genetic and environmental risk factors. The strongest genetic risk factors for many autoimmune diseases are those associated with the HLA loci on human chromosome 6. In the case of the IIM, the HLA A1;B8;Cw7;C4A*Q0;DRB1*0301;DQA1*0501 haplotype has been most strongly linked to myositis; however, different serologic, racial, and environmental exposure subgroups of IIM patients may have different genetic risk factors. Many non-HLA genes have also been shown to contribute to autoimmunity. Family and molecular genetic studies support the notion that these are polygenic diseases with incomplete penetrance requiring environmental triggering.

In light of present evidence, we propose a concept, consistent with all available data for the development of autoimmune diseases, that we refer to as the elemental disorder hypothesis (Fig. 2). In this hypothesis, each rheumatic disease, as defined by current clinico-pathologic criteria, is actually a collection of many elemental disorders. An elemental disorder would be defined as the minimal necessary and sufficient environmental exposures and genes that need to be present in the same individual to induce the pathology that results in a given sign–symptom complex. The environmental risk factors in this hypothetical construct could be single exposures or multiple sequential or concomitant exposures. The genetic risk factors for autoimmunity would consist of two forms: those that are common to many autoimmune diseases and those that are specific for a given elemental disorder.

The elemental disorder hypothesis is consistent with the finding that within a given autoimmune disease, different subgroups of patients can be defined through cluster analyses that share common clinical features, serologies, genetics, and pathogenic processes [55,70–72]. Furthermore, the finding that genetic risk factors for environmentally-associated rheumatic diseases often differ from risk factors for similar idiopathic rheumatic diseases supports the elemental disorder hypothesis [4]. It is also consistent with the observation that when the same autoimmune disease occurs within a family, affected members are likely to have a similar form of the disease [28,29,51•,73], because family members would be more likely to share common environmental and genetic risk factors. Additionally, this hypothesis could explain how the same pattern of autoimmune diseases in

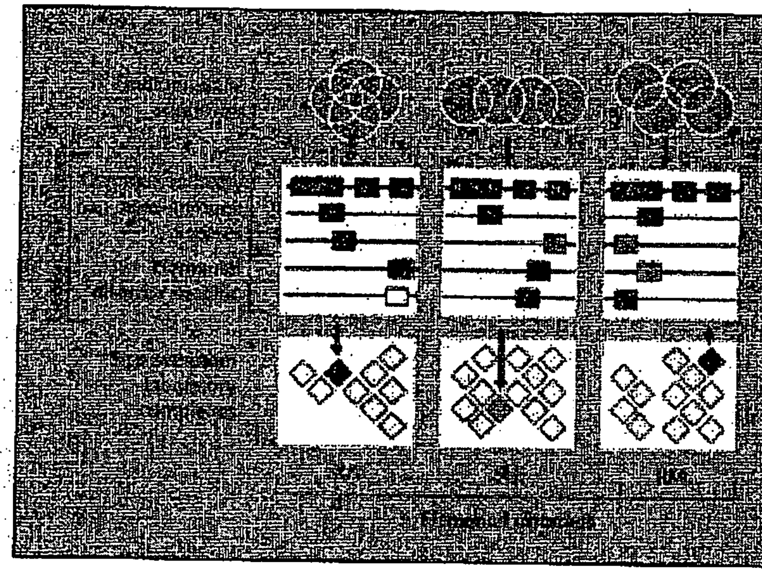

Figure 2. Possible mechanisms by which autoimmune diseases and familial autoimmunity may arise—the elemental disorder hypothesis. Each autoimmune disease, as currently classified, is in this view a heterogeneous collection of clinical signs, symptoms and laboratory findings composed of many elemental disorders. Elemental disorders are defined by the minimal necessary and sufficient environmental exposures and genes that need to be present in individuals to induce a common pathology that results in a given sign-symptom complex. Because family members are more likely to share both the genetic (the common autoimmunity predisposing and elemental disorder specific genes) and environmental risk factors that give rise to elemental disorders, the same elemental disorder would be expected to been seen more often in family members with the same disease.

pedigrees would occur, regardless of which autoimmune disease was studied in the proband, because the frequency of each elemental disorder would depend on the prevalence of its genetic and environmental risk factors in a given population. The probability that multiple elemental disorders likely comprise each rheumatic disease, as defined today, is a major potential confounder of epidemiologic, genetic, and therapeutic studies. Thus, the definition of these elemental disorders could have a major impact on the diagnosis, treatment, and possible prevention of many autoimmune diseases. A major challenge today is to develop new approaches and paradigms to overcome the many logistic and other barriers to understanding the complex pathogeneses of the autoimmune diseases.

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